

Hot Topics in Managing Syphilis

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SCHOOL *of* MEDICINE

Conflicts of Interest

- None

Objectives

- At the end of the presentation, attendees should be able to:
 - Describe the epidemiology of syphilis in Maryland and approaches to reducing reinfections
 - Interpret the reverse sequence testing algorithm for syphilis
 - Describe the situations where lumbar punctures are needed to diagnose neurosyphilis

Confusion

BRIEF REPORT

Question, response	No. (%) of providers who responded that they treated patients with syphilis				
	Overall ^a (n = 390 respondents)	0 patients (n = 32 respondents)	1–5 patients (n = 226 respondents)	6–20 patients (n = 105 respondents)	>20 patients (n = 23 respondents)
Use of dark-field microscopy					
Not available	304 (81)	14 (70)	190 (85)	77 (73)	20 (87)
Unsure if available	24 (6)	3 (15)	12 (5)	9 (9)	0 (0)
Available, but do not use	6 (2)	1 (5)	2 (1)	3 (3)	0 (0)
Use it	41 (11)	2 (10)	19 (9)	16 (15)	3 (13)
Diagnosis of primary syphilis					
Send RPR test to lab, treat patient	211 (56)	8 (42)	128 (57)	62 (59)	12 (52)
Send RPR test to lab, repeat if negative before treating patient	69 (18)	6 (32)	41 (18)	18 (17)	3 (13)
Send RPR test to lab, treat only if positive	62 (17)	3 (16)	38 (17)	14 (13)	6 (26)
Treat, no RPR test	8 (2)	1 (5)	4 (2)	3 (3)	0 (0)
Other	25 (7)	1 (5)	13 (6)	8 (8)	2 (9)
Benzathine penicillin treatment for secondary syphilis for patients with HIV infection					
Once	118 (31)	1 (5)	61 (27)	43 (41)	10 (44)
3 doses	233 (62)	16 (80)	150 (67)	53 (51)	13 (57)
Other	24 (6)	3 (15)	13 (6)	8 (8)	0 (0)
LP performed for asymptomatic secondary syphilis if CD4 ⁺ cell count is 150 cells/ μ L					
No	93 (25)	1 (6)	46 (21)	34 (32)	11 (48)
Yes	242 (65)	16 (89)	145 (65)	68 (65)	11 (48)
Uncertain	39 (10)	1 (6)	33 (15)	3 (3)	1 (4)
LP performed for asymptomatic secondary syphilis if CD4 ⁺ cell count is 550 cells/ μ L					
No	193 (54)	2 (11)	109 (52)	65 (64)	15 (65)
Yes	157 (44)	15 (83)	95 (45)	37 (36)	8 (35)
Uncertain	7 (2)	1 (6)	6 (3)	0 (0)	0 (0)
Highest titer willing to follow for HIV-negative patient					
<1:4	88 (28)	7 (50)	51 (27)	24 (26)	6 (27)
1:4	99 (31)	3 (21)	70 (37)	22 (24)	4 (18)
>1:4	131 (41)	4 (29)	68 (36)	47 (51)	12 (55)
Highest titer willing to follow for HIV-positive patient					
<1:4	135 (41)	11 (73)	85 (44)	29 (31)	8 (37)
1:4	94 (29)	3 (20)	56 (29)	29 (31)	5 (23)
>1:4	98 (30)	1 (7)	51 (27)	37 (39)	9 (41)

Dilemmas in the Management of Syphilis: A Survey of Infectious Diseases Experts

Deborah Dowell,^{1,2} Philip M. Polgreen,⁴ Susan E. Beekmann,⁴ Kimberly A. Workowski,^{2,3} Stuart M. Berman,¹ and Thomas A. Peteman¹

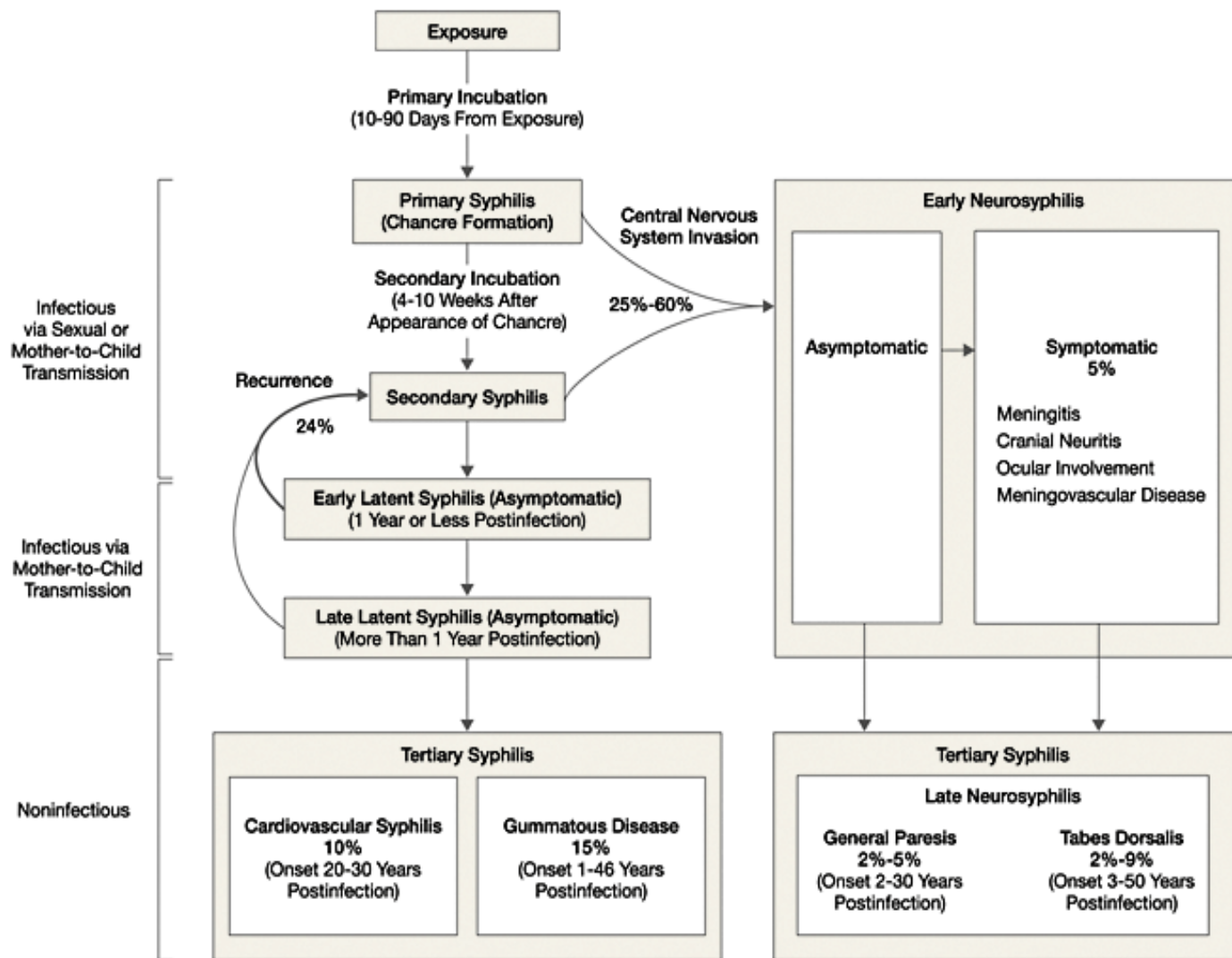
¹Epidemic Intelligence Service, Office of Workforce and Career Development, and ²Epidemiology and Surveillance Branch, Centers for Disease Control and Prevention, and ³Department of Infectious Diseases, Emory University, Atlanta, Georgia; ⁴Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa

EDITORIAL COMMENTARY

When Guidelines Don't Guide the Physician

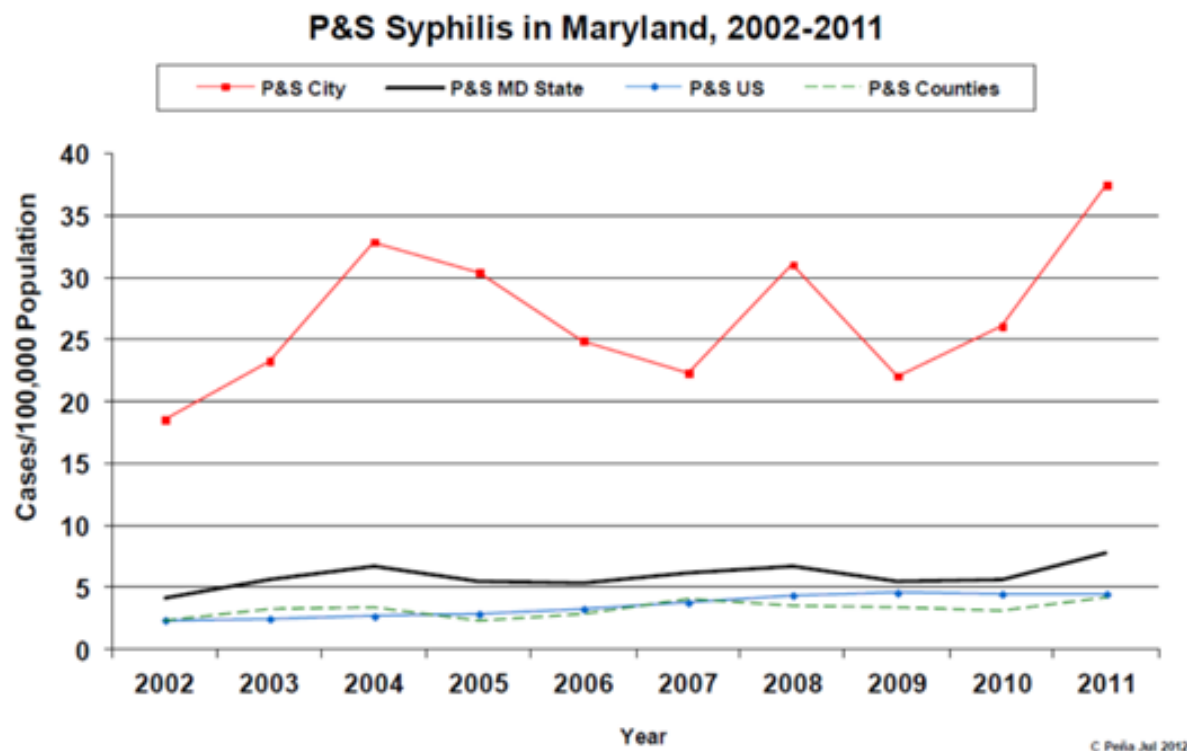
Peter A. Gross

Hackensack University Medical Center, Hackensack, New Jersey
JGIM



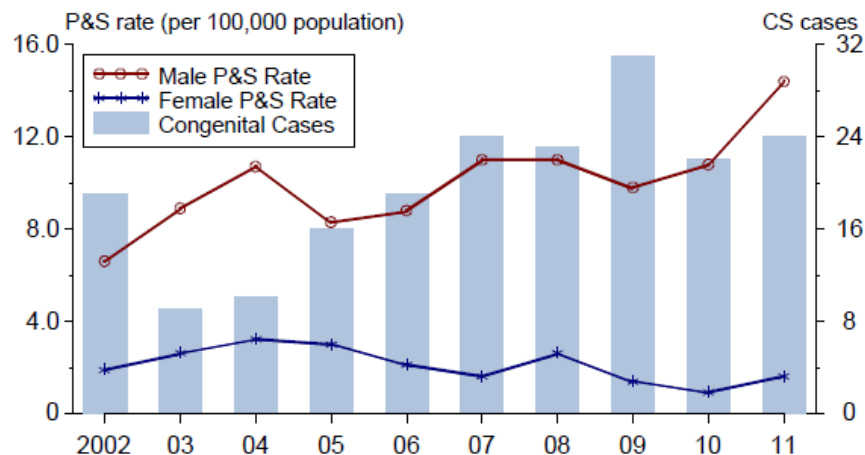
Syphilis in MD

- 2010: 285 early syphilis (ES) cases reported
- 2011: 424 ES cases reported

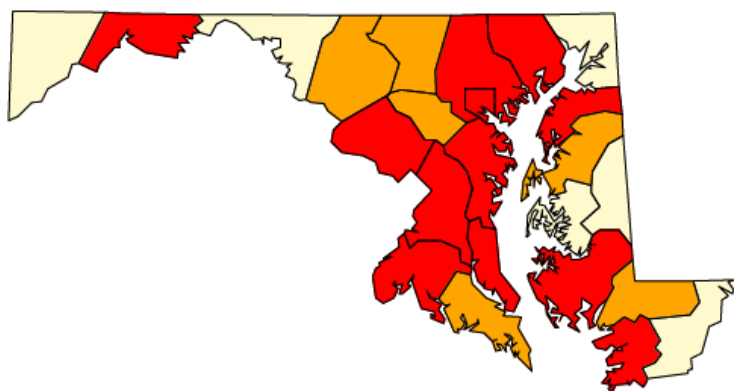


Who's Getting Syphilis in MD?

Syphilis: P&S Rates and Congenital Cases, Maryland, 2002 – 2011



Total P&S Syphilis Rates by County, Maryland, 2011



Rate (per 100,000 population)

≤0.4 0.41 - 2.2 >2.2

Primary and secondary syphilis

- **CASES:** Maryland reported 452 cases in 2011.
- **RATES:** Maryland ranked 3 among 51 areas (48 states; Washington, DC; and 2 territories) reporting at least one case of P&S syphilis with 7.8 cases per 100,000 population compared to the U.S. rate of 4.5 cases per 100,000 population.

Rates of primary and secondary syphilis, by sex

- In Maryland, the rate among males was 14.4 per 100,000 population compared to the U.S. male rate of 8.2 per 100,000.
- The rate among females was 1.6 per 100,000 compared to the U.S. female rate of 1.0 per 100,000.

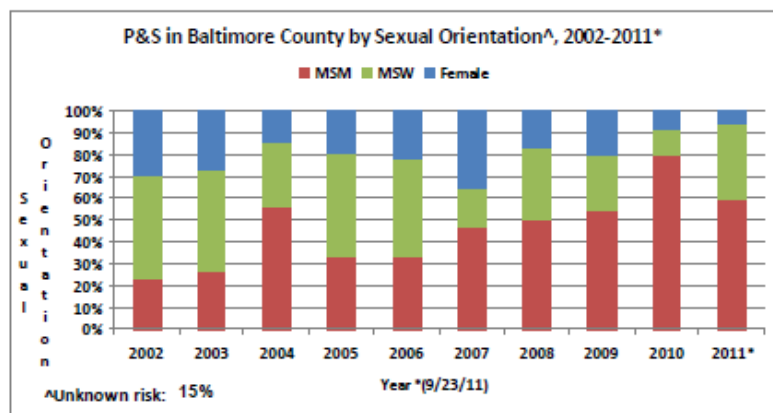
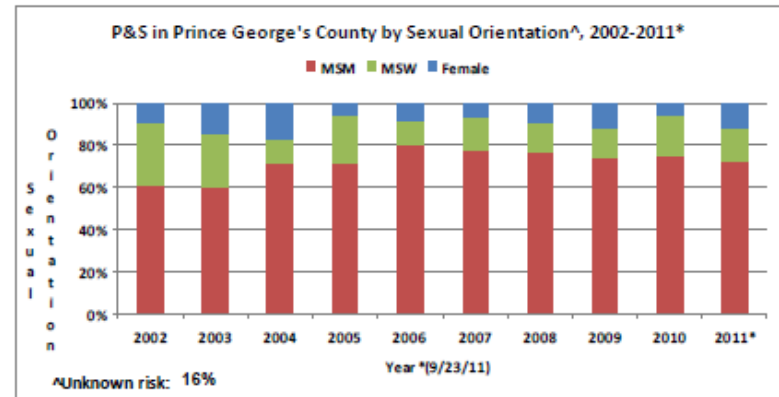
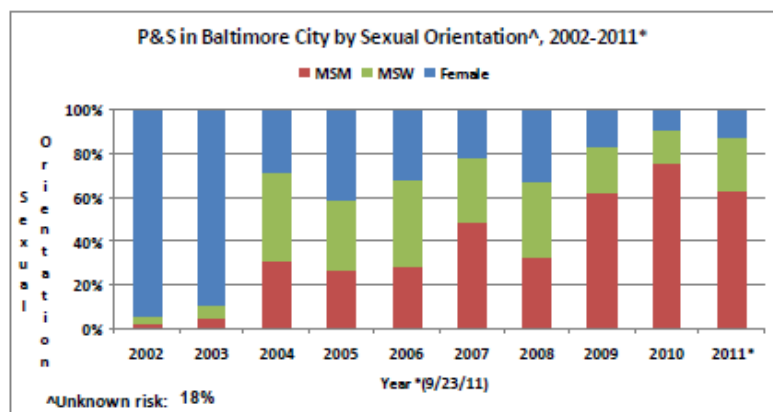
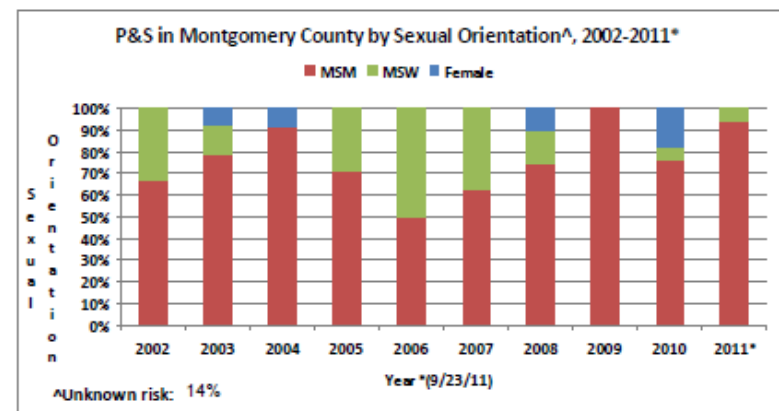
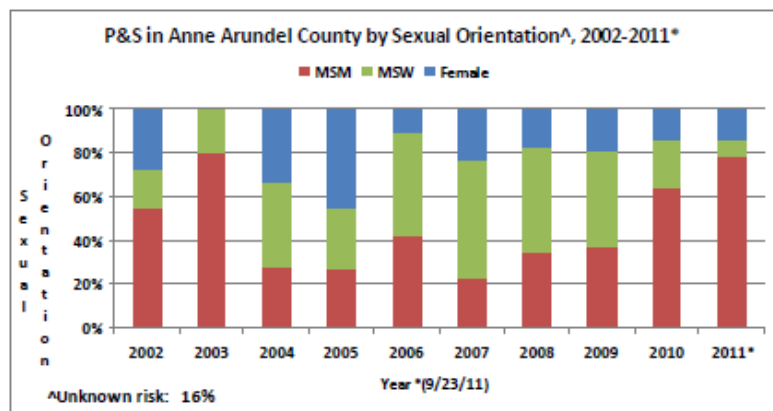
Rates of primary and secondary syphilis, by race/ethnicity

- In Maryland, the race/ethnicity adjusted rates per 100,000 population were 2.0 among whites, 20.9 among blacks, 2.8 among Hispanics, 1.2 among Asian/Pacific Islanders, and 0.0 among American Indians/Alaska Natives.
- The rate among blacks was 10.5 times that of whites.
- The rate among Hispanics was 1.4 times that of whites.

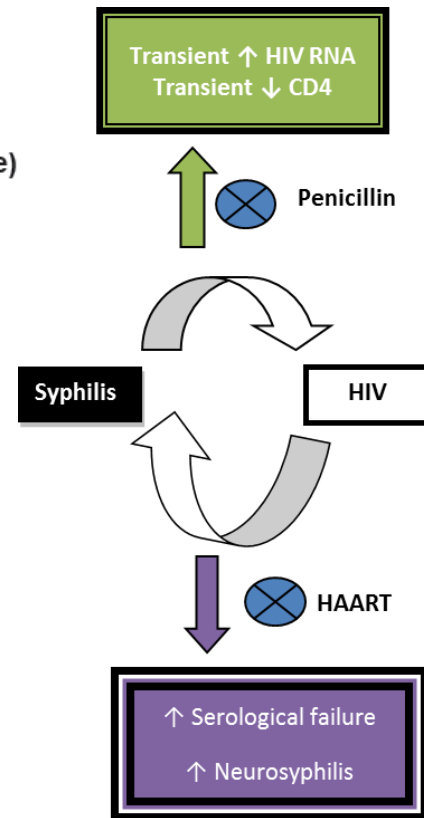
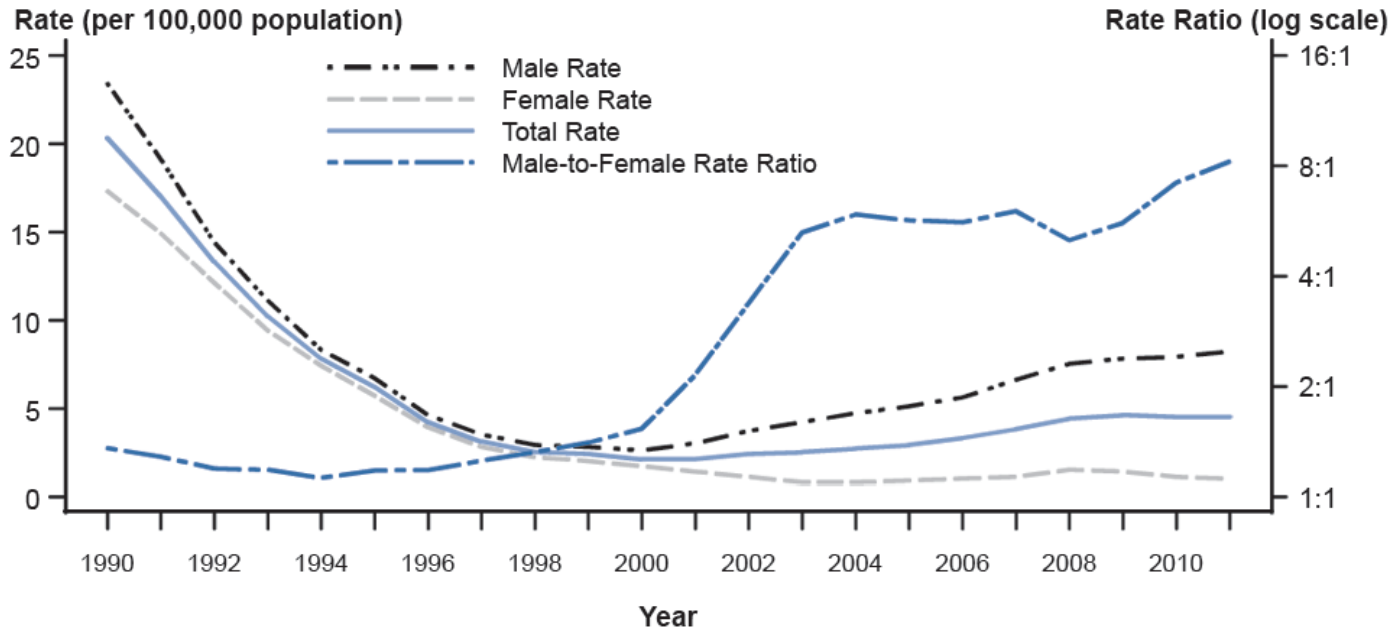
Congenital syphilis

- **CASES:** Maryland reported 24 cases in 2011.
- **RATES:** Maryland ranked 2 among among 25 areas (23 states; Washington, DC; and 1 territory) reporting at least one case of congenital syphilis with a rate of 31.1 cases per 100,000 live births compared to the U.S. rate of 8.5 cases per 100,000.

Diagnosis (YTD – 2013)	Male	Female
Primary syphilis	6	0
Secondary syphilis	33	8
Early latent syphilis	33	10



Syphilis & HIV



- According to data from BESURE (National HIV Behavioral Surveillance System), HIV positivity among MSM in Baltimore was 38% in 2008 and 43% in 2011
- In Maryland last year, 92 of 158 (58%) P&S cases with known status were HIV infected [data courtesy of Cesar Pena, DHMH]

Syphilis Reinfection

- **23%** of MSM diagnosed with early syphilis from 2010-2011 had been diagnosed with syphilis in the preceding 4 years

[Epi-Aid 2013-030: Laura Cooley, MD, MPHTM Alexa Oster, MD; Christine Ross, MD, MPHTM; Geoff Hart-Cooper]

- **30%** of HIV-infected persons with syphilis enrolled in the Johns Hopkins Clinical Cohort were retreated for syphilis within 5 years

CID 2008; 47:258–65

What can we do?

- Every 3-month screenings among highly active MSM is very high-yield and cost efficient. Contact tracing is high-yield but costly. Screening in jails also appeared to be cost efficient.

Gray RT, et al. *STD* 2010; 37:298-305; Lewis, FMT, et al. *J Publ Health Management Practice* 2011; 17:513-21

- Mathematical models suggest that changes in behaviors and condom use, particularly short-term ones (and even long-term ones if they were only modest) would not impact syphilis rates and that **frequent screening** among very high risk individuals is probably what would have the most impact.

Gray RT, et al. *STD* 2011;38: 1151-1158

- About 30% of high-risk MSM were not rescreened in the 6 months following therapy for syphilis.

Marcus JL, et al. *STD* 2011; 38:24-29

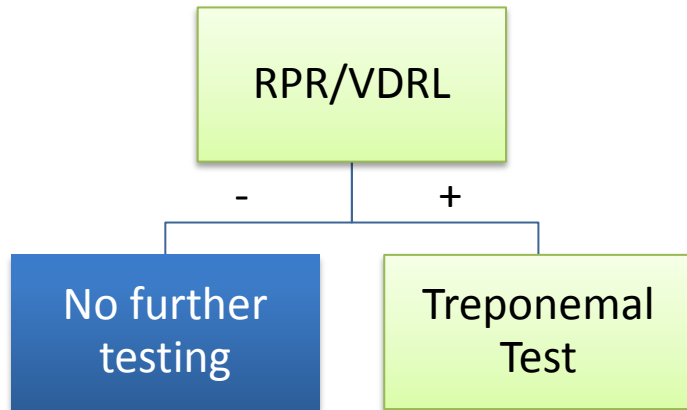
Is More Penicillin Better in Early Syphilis?

- 579 HIV-infected participants with early syphilis from 7 hospitals in Taiwan between 2007 and 2012.
 - BPG 2.4 MU X1 (N=302) vs. BPG 2.4 MU X3 (N=277)
 - 70.9% serological responses in BPG X1 group vs. 76.7% in BPG X3 group

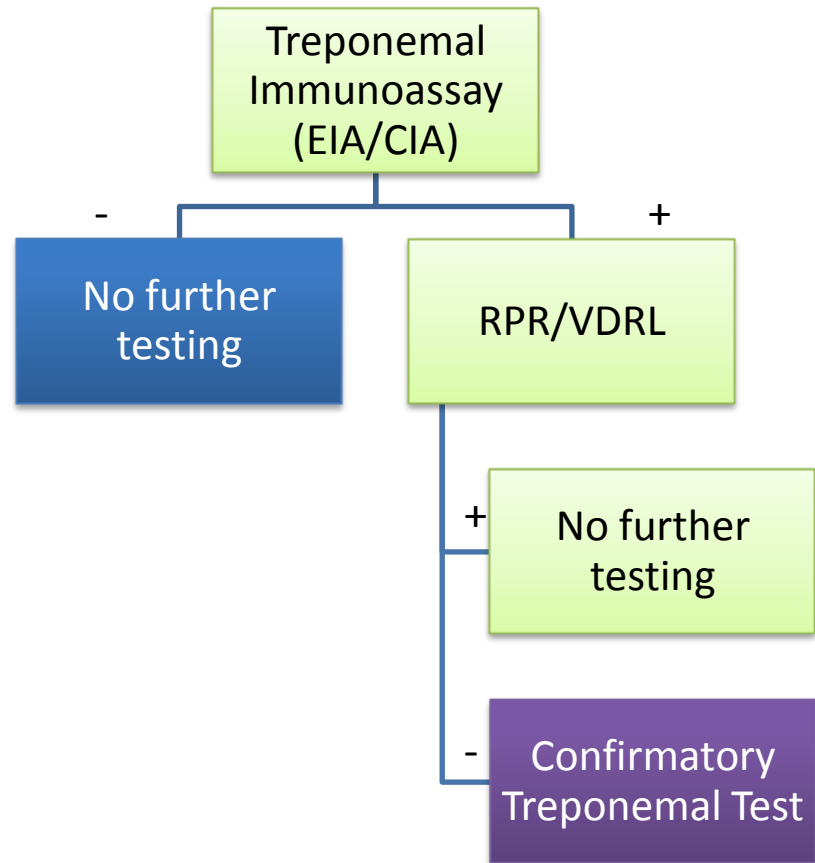
More is NOT better

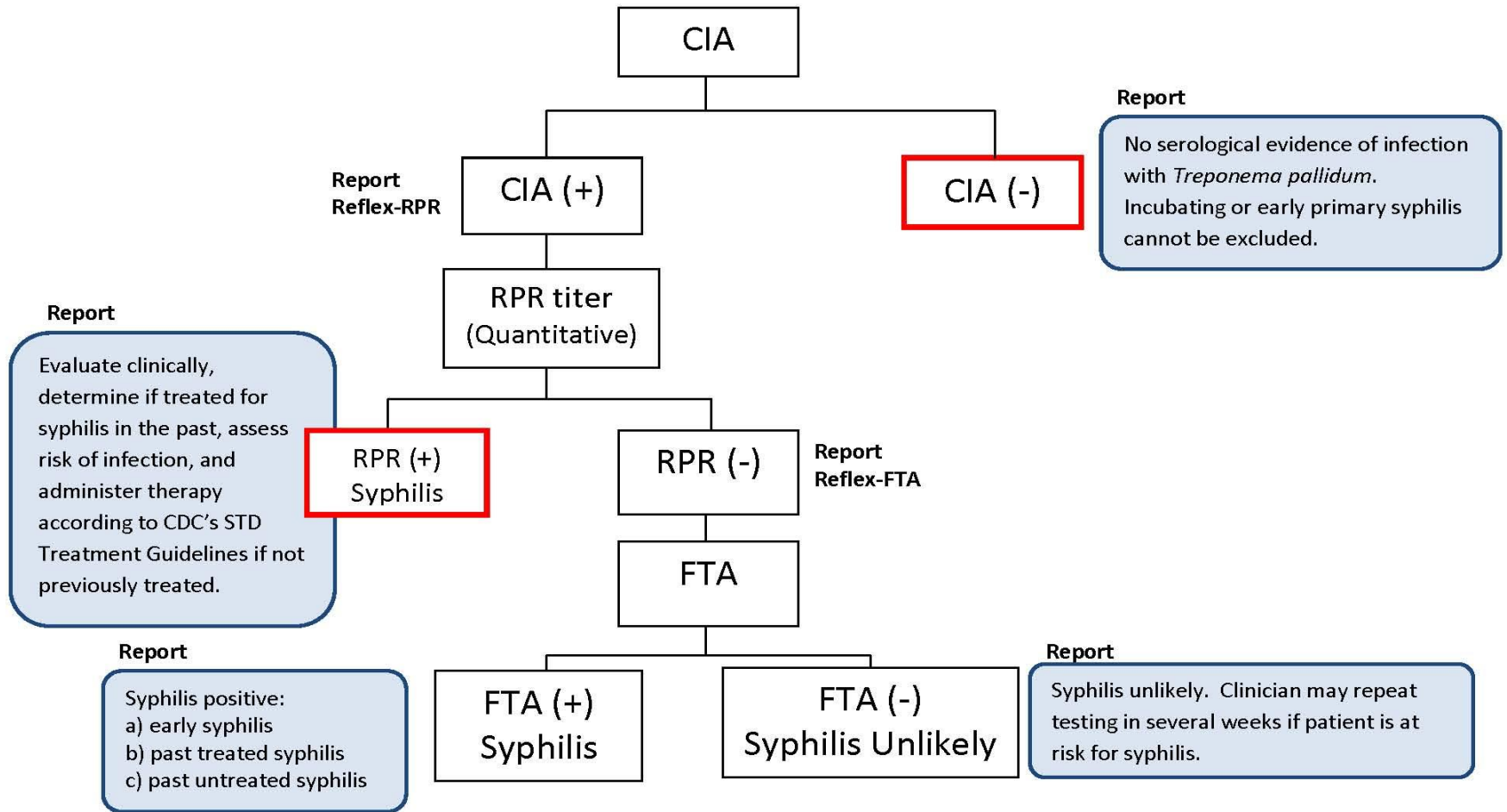
Serological Testing for Syphilis

Traditional Algorithm



Reverse Sequence Algorithm





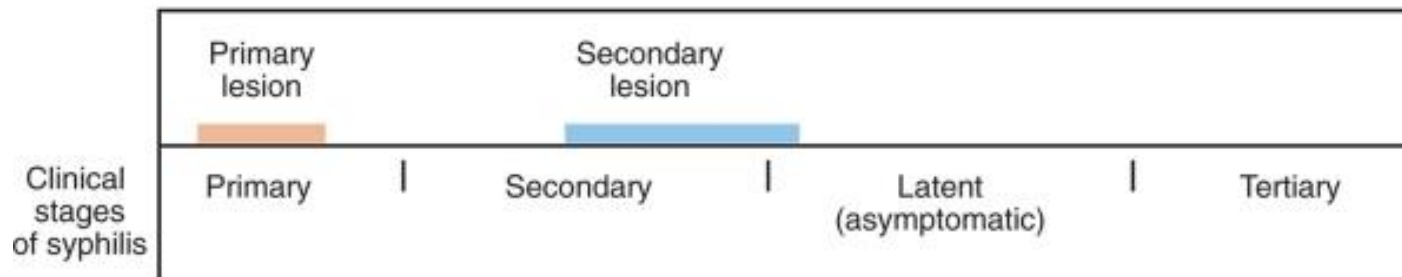
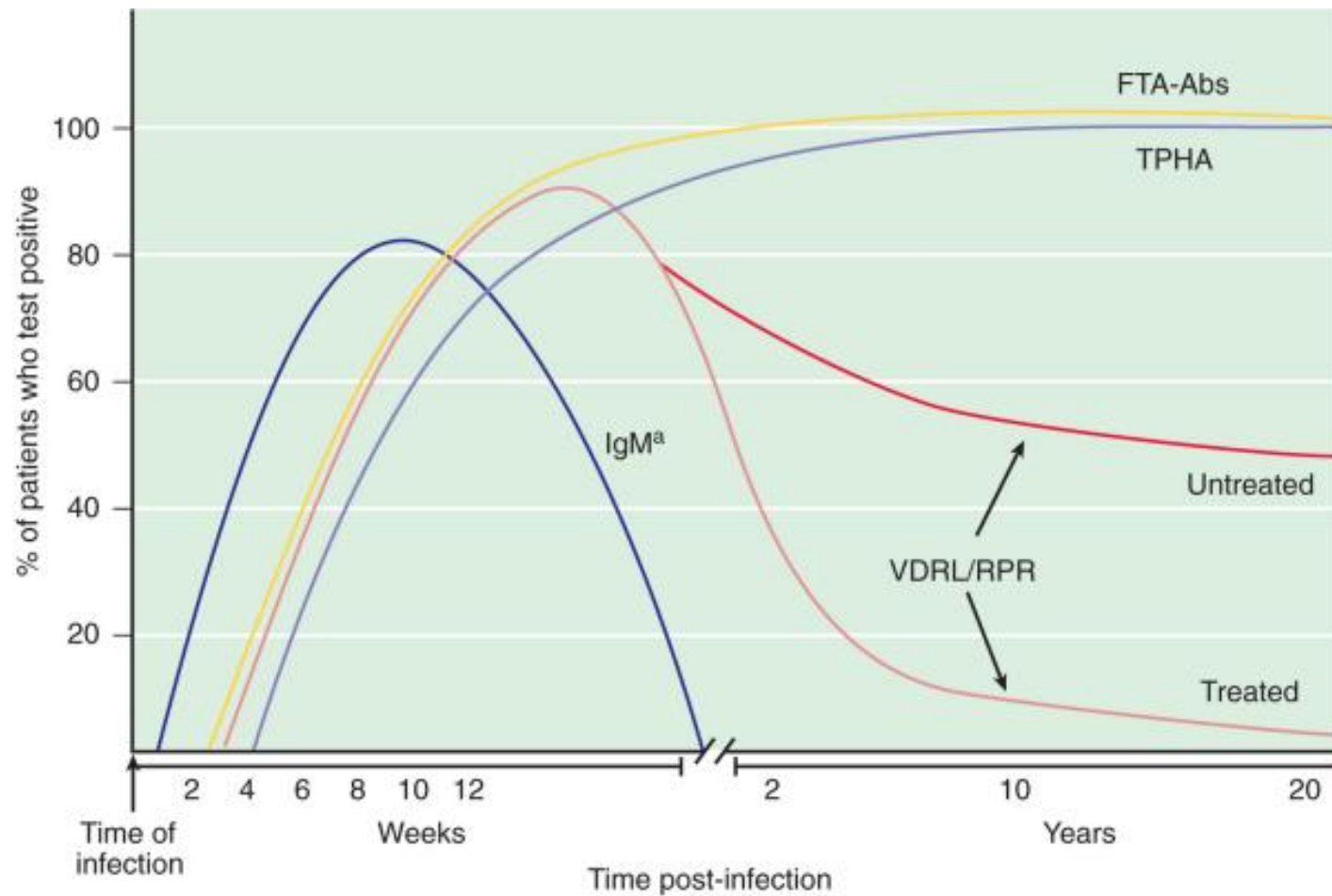
Dr. Barbara Detrick

Immunology Laboratory

The Antibodies

Serological Tests For Syphilis

Non-treponemal Tests	Treponemal Tests
<p>Complement fixation tests</p> <ul style="list-style-type: none"> - Wasserman reaction <p>Flocculation Tests</p> <ul style="list-style-type: none"> - Rapid Plasma Reagin (RPR) - VDRL - TRUST 	<p><i>Treponema pallidum</i> immobilization assay (TPI)</p> <p>Fluorescent treponemal antibody absorption (FTA-ABS)</p> <p><i>Treponema pallidum</i> hemagglutination assay (TPHA)</p> <p><i>Treponema pallidum</i> passive particle agglutination assay (TPPA)</p> <p>Enzyme Immunoassay (EIA)</p> <p>Western Blot (WB) and Pseudoblots</p> <p>Automated Chemiluminescence platforms</p> <p>Chromatographic Point of Care (POC) tests</p> <p>Microsphere Immunoassay</p>



Sensitivity and Specificity of Serologic Tests for Syphilis

Test	Sensitivity during stage of infection, % (range)				Specificity, % (range)
	Primary	Secondary	Latent	Late	
Nontreponemal tests					
VDRL [14]	78 (74–87)	100	96 (88–100)	71 (37–94)	98 (96–99)
TRUST [14]	85 (77–86)	100	98 (95–100)	NA	99 (98–99)
RPR [14]	86 (77–99)	100	98 (95–100)	73	98 (93–99)
Early treponemal tests					
MHA-TP [15]	76 (69–90)	100	97 (97–100)	94	99 (98–100)
TPPA [16]	88 (86–100)	100	100	NA	96 (95–100)
TPHA [17]	86	100	100	99	96
FTA-ABS [14]	84 (70–100)	100	100	96	97 (94–100)
Enzyme immunoassays					
IgG-ELISA [18]	100	100	100	NA	100
IgM-EIA [19]	93	85	64	NA	NA
ICE [20]	77	100	100	100	99
Immunochemiluminescence assays					
CLIA [21]	98	100	100	100	99

NOTE. CLIA, chemiluminescence assay; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; FTA-ABS, fluorescent treponemal antibody absorption assay; ICE, immune-capture EIA; MHA-TP, microhemagglutination assay for *Treponema pallidum*; NA, not available; TPHA, *T. pallidum* hemagglutination assay; TPPA, *T. pallidum* particle agglutination; TRUST, toluidine red unheated serum test.

False Positive Serological Tests

- Lipoidal (RPR or VDRL)
 - Age
 - Pregnancy
 - Other infections (particularly viral)
 - Autoimmune diseases
- Treponemal
 - Other pathogenic treponematoses (yaws, pinta)
 - Non-pathogenic treponemes associated with necrotizing gingivitis and chronic periodontitis*
 - Lyme disease
 - Autoimmune diseases (rare)

Nontreponemal Serologic Tests

Advantages

- Rapid and inexpensive
- Can be done in clinic or office
- Quantitative
- Used to follow response to therapy
- Can be used to evaluate possible reinfection

Disadvantages

- May be insensitive in certain stages
- False-positive reactions may occur
- Prozone effect may cause a false-negative reaction
- Require laboratory technician to perform test and interpret results

Treponemal Serologic Tests

- Principles
 - Measure antibody directed against *T. pallidum* antigens
 - Qualitative (positive or negative)
 - Usually reactive for life (but may disappear over time)
- Treponemal tests include TP-PA, MHA-TP, FTA-ABS, ELISA, CIA

Advantages of RSA using CIA

- Efficiency
- Objectivity
- Cost-effectiveness in low prevalence settings
 - Increases specificity
 - Decreases laboratory tech time
- Comprehensive data

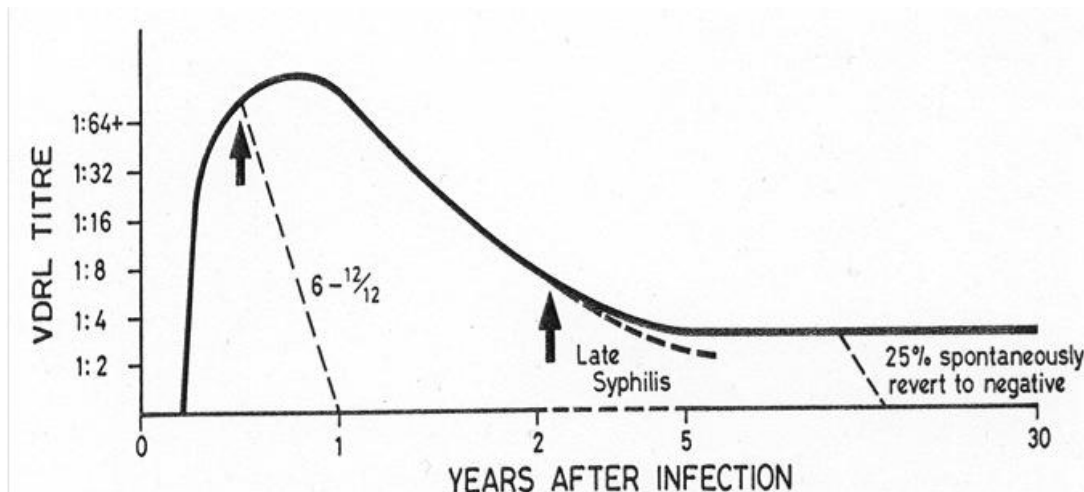
Positive Immunoassay & Negative RPR

Negative Confirmatory Treponemal Test

- False positive immunoassay
 - Be careful of pre-test probability

Positive Confirmatory Treponemal Test

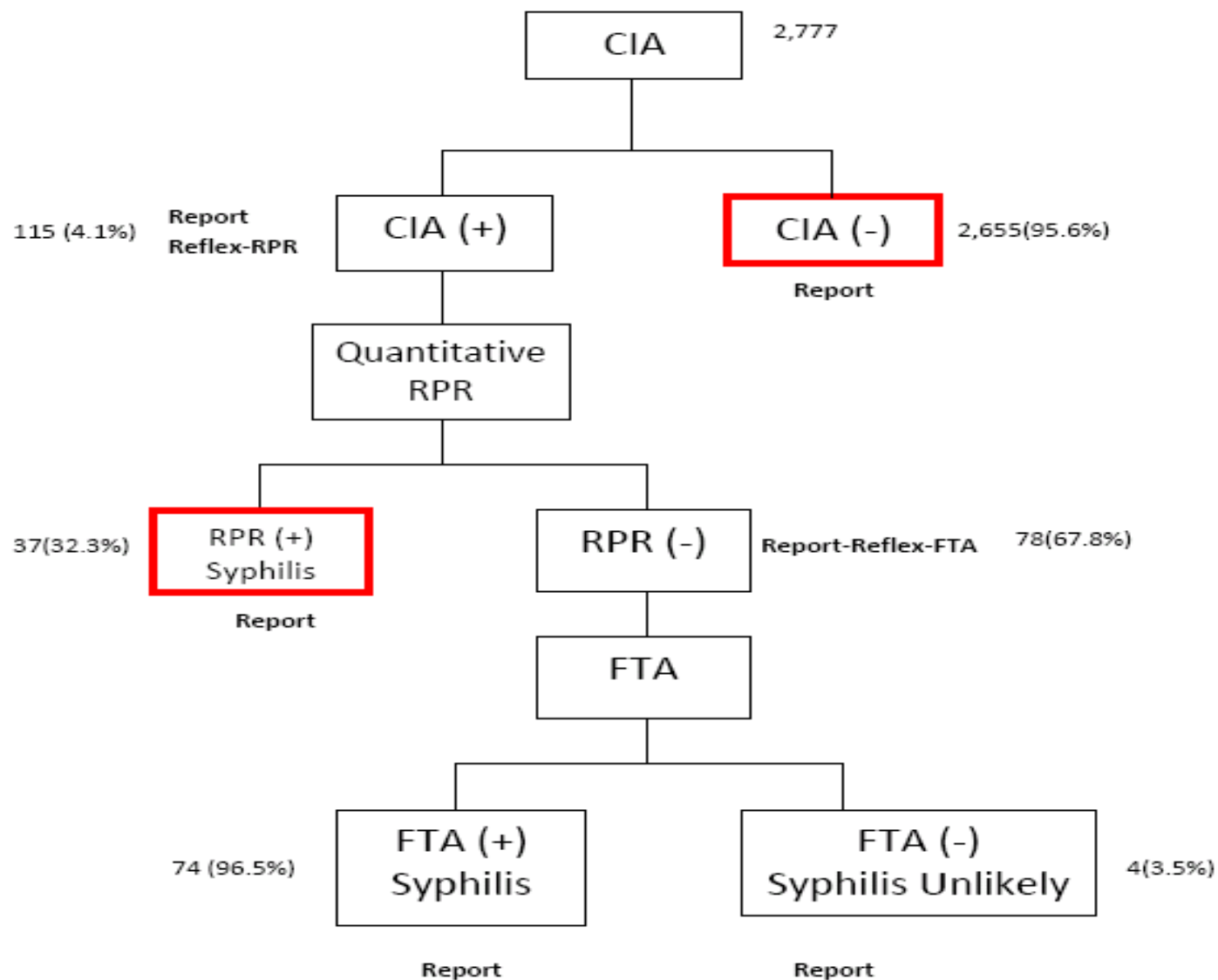
- Old treated syphilis
- Old untreated syphilis
- Early syphilis
- Prozone reaction



The Hopkins Experience

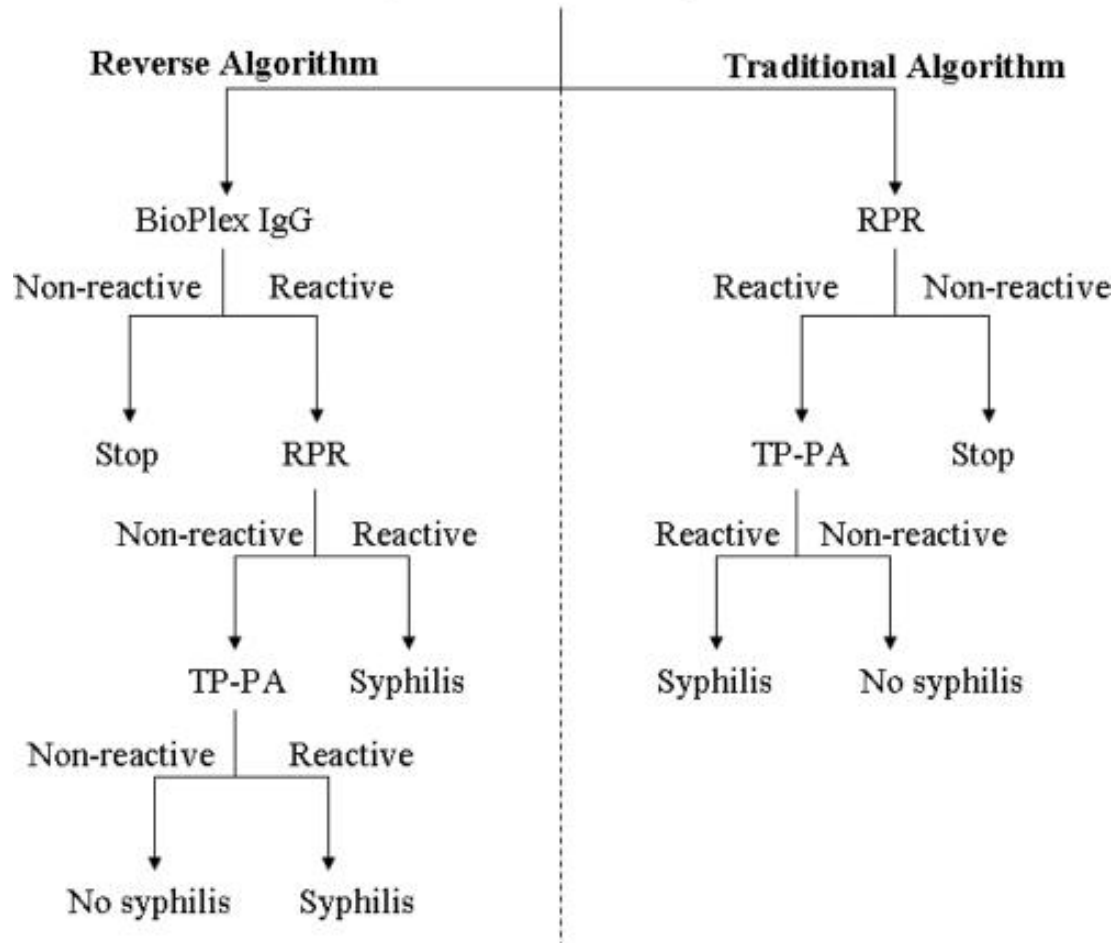
- 4000 serological tests for syphilis/month
- 4-6 false positive CIAs/ month
- 10 indeterminate CIAs/ month that require further testing

Johns Hopkins Hospital Algorithm for Syphilis Testing



Head-to-Head Comparison

1,000 serum samples



-Among the 1,000 samples tested, 15 were reactive by reverse screening compared to 4 by the traditional screening test

- More false-positives detected with reverse algorithm

6/15 tests were false +
0/4 tests were false +

- Reverse algorithm identified 2 patients with latent syphilis

Risks: Negative RPR/VDRL with Positive Treponemal Tests

- **Public Health Risks**
 - **Sexual transmission**
 - Significant for early syphilis
 - None for latent syphilis
 - **Vertical transmission**
 - Significant for early syphilis
 - Unclear for late syphilis in the RPR/VDRL era
 - A new study suggests that vertical transmission with a persistently negative RPR is unlikely
- **Risks to Individual**
 - Risk of complications (i.e. disease progression)

Clinical Cases: Is Ignorance Bliss?

50 year old asymptomatic newly divorced man with a past history of gonorrhea wants to be checked for sexually transmitted infections. Physical examination is normal.

CIA+ RPR- TPPA+

He denies ever being treated for syphilis

32 year old woman at 24 weeks of gestation (no prenatal care) is seen in a local ED for abdominal pain. Examination is said to be unremarkable. Sent home.

CIA+ RPR- TPPA+

Brought to STD Clinic where physical examination reveals a small painless vaginal ulcer that is darkfield positive. Patient treated for early syphilis.

Cost

- Costs to patients
- Cost Effectiveness
 - Cohort of 200,000: 1000 current infections and 10,000 previously treated infections
 - Reverse sequence algorithm treated 99% of the syphilis cases, but resulted in more overtreatment
 - Net cost per case treated was slightly higher for the reverse sequence algorithm (\$1671 vs. \$1621)

Outside the U.S.

GUIDELINE

IUSTI: 2008 European Guidelines on the Management of Syphilis

P French (Chair) FRCP, **M Gomberg** MD, **M Janier** MD PhD, **B Schmidt** MD, **P van Voorst Vader** MD and **H Young** MD

- A treponemal antigen test EIA or TPPA (preferred to TPHA) is recommended as a single screening test;
- The RPR/VDRL is not recommended as a primary screening test;^{4,36-38} It may be used for the rapid detection of symptomatic early syphilis in at-risk patients (supplemented with a standard recommended screening test). In these circumstances

Neurosyphilis

- There are **no established criteria** for the diagnosis of neurosyphilis
- Certain criteria that are used clinically:
 - Neurological symptoms
 - A positive CSF VDRL
 - Pleocytosis [>5 WBC/ml]
 - Elevated protein concentration [>50 mg/dl]

Current CDC Recommendations for Lumbar Puncture

- All **neurologically symptomatic** patients
- **Asymptomatic** patients with tertiary syphilis
- All neurologically **asymptomatic** patients who don't respond to therapy (i.e. lack of four-fold decline in RPR titers) and in whom reinfection is ruled out
- HIV+ patients with a CD4 count ≤ 350 cells/ml or RPR titer $\geq 1:32$ are more likely to have CSF pleocytosis

A Failure of Prevention...

- Although some important unanswered questions persist and are the source of continued controversy, the lack of definitive answers to these questions is NOT the cause of increasing syphilis rates
- Aggressive primary and secondary prevention measures which are not controversial, which have been recommended since the dawn of the HIV epidemic, and which are critical to ensure successful responses are often not being implemented.

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